

substantially and selectively killing dividing cells, and/or (ii) killing dividing cells with less killing in quiescent endothelial cells, and/or (iii) selectively killing dividing endothelial cells and cancer cells compared to quiescent cells and/or (iv) controlling angiogenesis in an animal comprising administration of the said virus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.”

Applicants respectfully disagree with the Examiner on this point. For instance, Applicants refer the Examiner to Example 3, on page 18 of the specification, wherein Applicants describe, in some detail, an in vivo experiment which shows the selective killing of dividing cells (tumor cells) that have been injected with an E1A-CR2 Rb binding site mutant adenovirus. Further, Example 4 goes beyond the results shown in Applicants’ Example 3, in that it shows data from a cotton rat, which is permissive for adenoviral replication, that the E1A-CR2 Rb binding site viruses have limited, or no, killing capacity for quiescent normal cells.

Thus, the results in Examples 3 and 4 clearly show that Applicants’ methods are enabled for the claimed in vivo applications of the instant E1A-CR2 Rb mutant viruses. And, most importantly, that these viruses show selective in vivo killing in the sense that they will kill dividing cells, cancer cells, but not quiescent normal cells.

To summarize, based on Applicants’ discussion presented above, Applicants’ E1A-CR2 Rb binding site mutant viruses clearly are enabled for the in vivo methods claimed by the Applicants, AND such viruses show selective killing for dividing cells (cancer cells), and much less so for non-dividing, or quiescent normal cells.

Clearly then, the only issue that remains to overcome the §112 rejection is to show selective killing by the instant E1A-CR2 Rb binding site mutant viruses for dividing normal cells, for example, endothelial cells. Here, Applicants refer the Examiner to Example 2, page 17 of the specification. There is shown an in vitro experiment where Applicants show that the E1A-CR2 Rb binding site mutants replicate in and kill, actively proliferating micro-vascular endothelial cells. It is important to note that such replication and killing is not observed, or observed at a much reduced level, in quiescent micro-vascular endothelial cells. Those latter results parallel those obtained in vitro. The Examiner is referred to Figure 2 of Applicants specification.

The question arises whether the experiment that was done in vitro (that experiment shown in Figure 2) wherein the instant viruses kill dividing but not quiescent micro-vascular endothelial cells, can be extrapolated to the in vivo setting. Applicants respectfully submit that a reasonably skilled practitioner of this art would easily embrace Applicants' in vitro data to be predictive of the in vivo setting since Applicants have shown, as have others, that the in vitro model systems used in the field of oncolytic viruses can predict the in vivo killing properties of adenoviruses. The Examiner is referred to U.S. Patent No. 5,998,205 (Generic Therapeutics, Inc.) and U.S. Patent No. 5,698,443 (Calydon, Inc.). There are also many scientific publications that describe oncolytic adenoviruses and their killing properties. Two are: Journal of Virology, July 2000, page 6147, titled "Tumor-Specific Replication-Competent Adenovirus Vectors Overexpressing the Adenovirus Death Protein," and the Journal of Virology, March 2001, page 2857, titled "Replicating Adenoviruses that Target Tumors with Constitutive

Activation of the WNT Signaling Pathway.” In addition, the Examiner should know that there are many other such papers, and if requested to do so, Applicants will provide them to the Examiner. Applicants have enclosed herewith the two Journal of Virology papers.

In light of the foregoing discussion, Applicants respectfully submit that Applicants’ claims are enabled, and respectfully request that the Examiner withdraw the §112 rejection.

### 35 U.S.C. §103 Rejections

Claims 21-28 stand rejected under §103(a) as being unpatentable over Bischoff et al. (U.S. Patent No. 6,080,578) in view of Whyte, P. et al., Jelsma T.N. et al. and Moran et al. The Examiner has admitted that Bischoff et al. does not disclose the Applicant’s specific adenoviral mutants, namely dl922/947, dl1107 and pm928. The Examiner has stated that these viruses are, however, disclosed by Whyte et al., Jelsma et al. and Moran et al. The Examiner has combined Bischoff et al., with Whyte et al., Jelsma et al. and Moran et al. to state that “one of ordinary skill in the art would have been motivated to combine the teachings of Bischoff, Whyte, Jelsma and Moran whereby adenoviruses comprising an E1A locus encoding a mutant E1A protein that lacks a CR1 and/or CR2 domain thereby being incapable of binding RB in compositions comprising the adenovirus (see Bischoff abstract) to include such limitations as was taught by Whyte, Jelsma and Moran SO THAT MORE ADENOVIRUSES ARE AVAILABLE FOR SELECTIVELY KILLING NEOPLASTIC OR DIVIDING CELLS IN A MIXED CELL POPULATION.”

Applicants respectfully disagree with the §103(a) rejection for the following reasons. The Examiner is using hindsight to reject Applicants' claims, which, of course, is not permitted to support a §103(a) rejection. For instance, the Examiner has stated that "based on the cited references one skilled in the art would have more adenoviruses...available for selectively killing neoplastic or dividing cells in a mixed cell population." Applicants respectfully submit that only by reading Applicant's specification as the Examiner has done, would one skilled in the art be motivated to identify and develop such viruses as compositions, as claimed by the Applicants in claims 21-28. Thus Applicants respectfully submit that the Examiner is applying references that, absent hindsight, could not be used to support a §103(a) rejection. Thus, Applicants respectfully submit and request that the rejection be withdrawn.

In the Drawings,

A LETTER TO OFFICIAL DRAFTSPERSON is submitted herewith, attaching corrected Fig(s). 3C-4B drawing sheets. Subject to the approval of the Examiner, it is respectfully requested that the new drawing sheets be substituted for the originally filed drawing sheets for Fig(s) 3C-4B.

The Commissioner is authorized to charge any fees for a large entity associated with this response to Deposit Account No. 15-0615 for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

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